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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|------------------------------|------------------------|
| 10/789,222 | 02/27/2004 | Qin Yu | UPN0003-100 | 9718 |
| 34136 | 7590 | 11/16/2007 | | |
| Pepper Hamilton LLP 500 Grant Street One Mellon Bank Center, 50th Floor Pittsburgh, PA 15219-2502 | | | EXAMINER ROBINSON, HOPE A | |
| | | | ART UNIT 1652 | PAPER NUMBER |
| | | | MAIL DATE 11/16/2007 | DELIVERY MODE PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/789,222

Applicant(s)

YU, QIN

Examiner

Hope A. Robinson

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 10 October 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☐ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: 1 and 2.
Claim(s) objected to: _____.
Claim(s) rejected: 19, 26, 53 and 54.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See the attached sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

HOPE ROBINSON
PRIMARY EXAMINER

Hope A. Robinson
Primary Examiner
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DETAILED ACTION

Application Status

1. Applicant's response to the Office Action mailed August 10, 2007 on October 10, 2007 is acknowledged.

Claim Disposition/Election

2. Claims 1-2, 19, 26 and 53-54 are pending and are under examination

Maintained and Amended-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 19, 26 and 53-54 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to a pharmaceutical composition comprising a mutant Ang-1 protein. The claims read on a genus of fragments/variants since there is no structural limitation. No correlation is made between structure and function. Therefore the claims encompass a large variable genus of protein fragments and the specification lacks adequate written description to demonstrate to a skilled artisan that applicant was in possession of the claimed invention. Therefore, the skilled artisan cannot envision the detailed chemical structure of the protein fragments.

The specification fails to provide any additional representative species of the claimed genus to show that applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, disclosure of drawings, or by disclosure of relevant identifying characteristics, for example, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991), states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is,

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for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993).

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

4. Claims 19, 26 and 53-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the protein set forth in SEQ ID NO: 1, does not reasonably provide enablement for any fragment thereof or any homologous peptide thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors

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include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)).

The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of fragments thereof for the Ang-1 protein. No correlation is made between function and structure for the claimed protein (see for example claim 19). Therefore, the claims encompass variants/fragments that may not have any biological activity. Due to the large quantity of experimentation necessary to generate the infinite number of variants/fragments recited in the claims and possibly screen same for activity and the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance

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has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, *Biochemistry*, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments/variants encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (*J. Bacteriology*, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page

2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention.

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of variants/fragments or any homologous protein. The claims broadly read on any fragment thereof for the given sequence (SEQ ID NO: 1). The issue in this case is the breadth of the claims in light of the predictability of the art as determined by the

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number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

Response to Applicant's Arguments:

5. Applicant's arguments have been fully considered but are not deemed persuasive for the

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following reasons. Note that the rejections under 35 U.S.C. 112, first paragraphs remains.

Applicant's state that the claims clearly refer to the subject matter that is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention pertaining to the written description. The claims as amended have reduced some of the issues, however, the claims still read on any fragment of the "Ang-1 protein set forth in SEQ ID NO:1. Although the protein has 20 residues, the comprising language does not limit the size of the fragments and note that the rejected claims do not recite a structural limitation to correlate structure with function.

Applicant traverses the enablement rejection stating that the claims as amended are enabled by the specification such that one skilled in the art could practice the claimed invention. Specifically claims 19, 26 and 53-55 is directed to a pharmaceutical composition comprising a mutant Ang-1 protein. The claims read on a genus of fragments/variants since there is no structural limitation. No correlation is made between structure and function (see for example claim 19, which is directed a pharmaceutical composition and carrier and a mutant Ang-1 having a prescribed activity with no structure). Thus, the rejection remains.

Conclusion

6. No claims are presently allowable.

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7. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS 

Primary Examiner